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(REV. 5-93)

U.S. DEPARTMENT OF COMMERCE
PATENT AND TRADEMARK OFFICE

ATTORNEY'S DOCKET NUMBER
2013/1E251-US1

#3

TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US)

INTERNATIONAL APPLICATION NO.	INTERNATIONAL FILING DATE	PRIORITY DATE CLAIMED
PCT/US98/19420	28 May 1999	28 May 1999

TITLE OF INVENTION

FREQUENCY ESTIMATION OF ELECTRO-ISLET GRAPHY

APPLICANT(S) FOR DO/EO/US

Dan CHARASH

Applicant herewith submits to the United States Designated/Elected office (DO/EO/US) the following items and other information:

1. [] This is a **FIRST** submission of items concerning a filing under 35 U.S.C. 371.

2. [X] This is a **SECOND** or **SUBSEQUENT** submission of items concerning a filing under 35 U.S. C. 371.

3. [X] This is an express request to begin national examination procedures (35 U.S.C. 371 (f)) at any time rather than delay examination until the expiration of the applicable time limit set in 35 U.S. C. 371 (b) and PCT Articles 22 and 39 (1).

4. [] A proper Demand for International Preliminary Examination was made by the 19th month from the earliest claimed priority date.

5. [] A copy of the International Application as filed (35 U.S. C. 371 (c) (2))
   a. [] is transmitted herewith (required only if not transmitted by the International Bureau).
   b. [] has been transmitted by the International Bureau
   c. [] is not required, as the application was filed in the United States Receiving Office (RO/US)

6. [] A translation of the International Application into English (35 U.S. C. 371 (c)2)).

7. [] Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371 (c)(3))
   a. [] are transmitted herewith (required only if not transmitted by the International Bureau).
   b. [] have been transmitted by the International Bureau.
   c. [] have not been made; however, the time limit for making such amendments has NOT expired.
   d. [] have not been made and will not be made.

8. [] A translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371 (c) (3)).

9. [X] An oath or declaration of the inventor(s) (35 U.S.C. 371(c)(4)).

10. [] A translation of the annexes to the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371 (c)(5)).

Items 11. to 16. below concern other document(s) or information included:

11. [] An Information Disclosure Statement under 37 CFR 1.97 and 1.98 (with reference).

12. [] An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.

13. [] A FIRST preliminary amendment.
    [X] A SECOND or SUBSEQUENT preliminary amendment.

14. [] A substitute specification.

15. [] A change of power of attorney an/or address letter.

16. [] Other items or information: **Verified Statement Claiming Small Entity Status**

EXPRESS MAIL CERTIFICATE
Date 7/20/00 Label No. EL638221683
I hereby certify that, on the date indicated above I deposited this paper or fee with the U.S. Postal Service & that it was addressed for delivery to the Commissioner of Patents & Trademarks, Washington, D.C. 20231 by "Express Mail Post Office to Addressee" service.
G. KARASZI
Name (Print)
G. Karaszi
Signature

07/24/2000 EPI4WN3D 00000021 09530654
01 FC:963 40.00 OP
02 FC:967 51.00 OP

U.S. APPLICATION NO. (if known sec 37 [illegible].1.50) 09/530[illegible]	INTERNATIONAL APPLICATION NO.: [illegible]/US99/11973	Attorney's Docket Number 2013/1E271-US1

17. [] The following fees are submitted:

	CALCULATIONS	PTO USE ONLY
Basic National Fee (37 CFR 1.492 (a)(1)-(5)): Search Report has been prepared by the EPO [] or JPO [] **$840.00**		
International preliminary examination fee paid to USPTO (37 CFR 1.482) **$670.00**		
No international preliminary examination fee paid to USPTO(37 CFR 4.482) but international search fee paid to USPTO (37 CFR 1.445 (a) (2)... **$690.00**		
Neither international preliminary examination fee (37 CFR 1.482) nor international search fee (37 CFR 1.445(a)(2)) paid to USPTO..... **$970.00**		
International preliminary examination fee paid to USPTO (37 CFR 1.482) and all claims satisfied provisions of PCT Article 33(2)-(4)....**XXXX**..... **$96.00**		
ENTER APPROPRIATE BASIC FEE AMOUNT =		**$96.00**
Surcharge of $130.00 for furnishing the oath or declaration later than []20 []30 months from the earliest claimed priority date (37 CFR 1.492(e)).	**$**	

Claims	Number Filed	Number Extra	Rate		
Total Claims	**27-20**	**7**	**7** X $18.00	**$126.00**	
Independent Claims	**2-3**	**0**	**0** X $78.00	**$**	
Multiple dependent claims(s) (if applicable)		+260		**$**	
			TOTAL OF ABOVE CALCULATIONS =	**$222.00**	
Reduction by 1/2 for filing by small entity, if applicable. Verified Small Entity statement must also be filed. (Note 37 CFR 1.9, 1.27, 1.28).				**$111.00**	
			SUBTOTAL =	**$111.00**	
Processing fee of **$130.00** for furnishing the English translation later the [] 20 [] 39 months from the earliest claimed priority date (37 CFR 1.492(f)).			+	**$**	
			TOTAL NATIONAL FEE =	**$111.00**	
Fee for recording the enclosed assignment (37 CFR 1.21(h)). the assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31). **$40.00** per property			+	**$40.00**	
			TOTAL FEES ENCLOSED =	**$151.00**	
			Amount to be refunded		**$**
			charged:		**$**

a. [] A check in the amount of **$151.00** to cover the above fees is enclosed.

b. [] Please charge my Deposit Account No.04-0100 in the amount of $ to cover the above fees.

c. [X] The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. 04-0100. A duplicate copy of this sheet is enclosed.

NOTE: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR 1.137(a) or (b)) must be filed and granted to restore the application to pending status.

SEND ALL CORRESPONDENCE TO:
Joseph B. Lerch
Darby & Darby P.C.
805 Third Avenue
New York, New York 10022-7513

SIGNATURE Joseph B. Lerch

NAME **Joseph B. Lerch**

REGISTRATION NO. **26,936**

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:

Dan CHARASH

Serial No.: t/b/a (U.S. National Phase of International Appln. No. PCT/US99/11973 filed on May 28, 1999)

Filed: concurrently herewith

For: FREQUENCY ESTIMATION OF ELECTRO-ISLET GRAPHY

VERIFIED STATEMENT CLAIMING SMALL ENTITY STATUS SMALL BUSINESS CONCERN

I hereby declare that I am

[] the owner of the small business concern identified below:
[X] an official of the small business concern empowered to act on behalf of the concern identified below:

NAME OF CONCERN: CARMEL BIOSENSORS LTD.
ADDRESS OF CONCERN: Matam Center, Haifa 31905 ISRAEL

I hereby declare that the above identified small business concern qualifies as a small business concern as defined in 13 CFR 121.12 and in 37 CFR 1.9(d), for purposes of paying reduced fees to the United States Patent and Trademark Office, in that the number of employees of the concern, including those of its affiliates, does not exceed 500 persons.

Definitions: For purposes of this statement, (1) the number of employees of the business concern is the average over the previous fiscal year of the concern of the persons employed on a full-time, part-time or temporary basis during each of the pay periods of the fiscal year, and (2) concerns are affiliates of each other when either, directly or indirectly, one concern controls or has the power to control the other, or a third party or parties controls or has the power to control both.

I hereby declare that rights under contract or law have been conveyed to and remain with the small business concern identified above with regard to the invention entitled FREQUENCY ESTIMATION OF ELECTRO-ISLET GRAPHY, by inventor(s) described in

[] the specification filed herewith

[X] U.S. National Phase of International Application No. PCT/US99/11973, filed **May 28, 1999**

[] Patent No. , issued .

If the rights held by the above identified small business concern are not exclusive, each individual, concern or organization having rights to the invention is listed below* and no rights to the invention are held by any person, other than the inventor, who could not qualify as an independent inventor under 37 CFR 1.9(c) if that person made the invention, or by any concern which would not qualify as a small business concern under 37 CFR 1.9(d), or a nonprofit organization under 37 CFR 1.9(e).

NOTE: Separate verified statements are required from each named person, concern or organization having rights to the invention averring to their status as small entitled (37 C.F.R. 1.27)

NAME:

ADDRESS:

[] INDIVIDUAL [] SMALL BUSINESS CONCERN [] NONPROFIT ORGANIZATION

I acknowledge the duty to file, in this application or patent, notification of any change in status resulting in loss of entitlement to small entity status prior to paying, or at the time of paying, the earliest of the issue fee or any maintenance fee due after the date on which status as a small entity is no longer appropriate. (37 C.F.R. §1.28(b))

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statement and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application, any patent issuing thereon, or any patent to which this verified statement is directed.

NAME OF PERSON SIGNING: PROF. YORAM PALTI

TITLE OF PERSON (IF OTHER THAN OWNER): PRESIDENT OF CARMEL BIOSENSOR

ADDRESS OF PERSON SIGNING: 51 RUTH STR. HAIFA. ISRAEL

SIGNATURE: Yoram Palti DATE: JUNE 12TH, 2000

2013/1E271US1

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:

Dan CHARASH

Serial No.: t/b/a (U.S. National Phase of International Appln. No. PCT/US99/11973 - filed on May 28, 1999)

Filed: Concurrently Herewith

For: FREQUENCY ESTIMATION OF ELECTRO-ISLET GRAPHY

PRELIMINARY AMENDMENT

Hon. Commissioner of
Patents and Trademarks
Washington, DC 20231

ATTN: Box PCT
DO/EO/US

Sir:

Prior to examination, applicant wishes to amend the above-identified application as follows:

IN THE CLAIMS:

Claim 3, line 1, delete "or 2".

Claim 4, line 1, delete "or 2".

Claim 13, delete "any one of claims 2" and substitute therefore --claim 1--.

Claim 16, line 1, delete "14 or".

Claim 18, line 1, delete "14 or".

Claim 19, line 1, delete "14 or".

Claim 20, line 1, delete "any one of claims" and substitute therefore --claim--.

Please add the following Claims:

21. The method of claim 1, wherein the events are signals produced by biological micro-structures which are displaced from their original environment.

22. The method of claim 1, wherein the events are signals produced by living cells.

23. The method of claim 1, wherein the estimating step includes an autocorrelation operation.

24. The system of claim 14, wherein the module for estimating includes components to perform an autocorrelation operation.

25. The system of claim 14, wherein the processor is constructed to perform a segmented autocorrelation process.

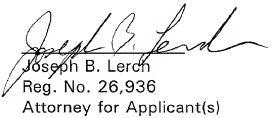
26. The system of claim 14, wherein the sensor is a probe capable of detecting signals emitted by living cells in the Islets of Langerhans, the frequency estimate being an indication of blood glucose level of a patient in which those cells are present

REMARKS

The claims have been amended to eliminate multiple claim dependencies and claims have been added to restore some of the dependencies.

Entry of this amendment is respectfully requested.

Respectfully submitted,



Joseph B. Lerch
Reg. No. 26,936
Attorney for Applicant(s)

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212-527-7700

EXPRESS MAIL CERTIFICATE

DATE 7/20/00 LABEL NO EL628221683

I HEREBY CERTIFY THAT, ON THE DATE INDICATED ABOVE I DEPOSITED THIS PAPER OR FEE WITH THE U S POSTAL SERVICE & THAT IT WAS ADDRESSED FOR DELIVERY TO THE COMMISSIONER OF PATENTS & TRADEMARKS, WASHINGTON, DC 20231 BY "EXPRESS MAIL POST OFFICE TO ADDRESSEE" SERVICE.

G KARASZI G Karaszi

NAME (PRINT) SIGNATURE

2013/1E271US1

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:

Dan CHARASH

Serial No.: 09/530,684

Filed: May 28, 1999

For: FREQUENCY ESTIMATION OF ELECTRO-ISLET GRAPHY

SECOND PRELIMINARY AMENDMENT

Hon. Commissioner of
Patents and Trademarks
Washington, DC 20231

ATTN: Box PCT
DO/EO/US

Sir:

Prior to examination, please amend the above-identified application as follows:

IN THE CLAIMS:

Claim 6, line 1, delete "or 2".

Please add Claim 27:

--27. (Amended) The method of claim 2, wherein the estimating step includes an auto correlation operation.--

REMARKS

Claim 6 has been amended to eliminate a multiple claim dependency and claim 27 has been added.

Entry of this amendment is respectfully requested.

Respectfully submitted,

Joseph B. Lerch
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09/530684

FREQUENCY ESTIMATION OF ELECTRO-ISLET-GRAPHY

Field of the Invention

The present invention relates generally to methods and systems for processing electro-physiological signals and, more particularly, concerns the detection and analysis of electrical activity related to blood glucose concentration.

Background of the Invention

Blood glucose level monitoring is of great importance for diabetics. Continuous monitoring of the glucose level can greatly reduce the medical complications, that are caused by metabolic imbalance.

The Islets of Langerhans are located in the pancreas, and are responsible for the manufacture of insulin in the human body. An islet is a cluster of many cells. The Beta cells within the islets respond to glucose in bursts of electrical activity. The use of such islets, derived from the pancreas of donor animals, in a blood glucose monitor is disclosed in U.S. Patent 5,101,814. Electro-Islet-Graphy (EIG) is the measurement of the electrical activity of the islets of Langerhans. The present invention utilizes EIG to provide a continuous blood glucose level sensor.

Studies demonstrate a clear correlation between the fundamental frequency of the EIG signal, and the glucose level in the medium surrounding the islet. Hence, the estimation of the fundamental frequency of Electro-Islet-Graphy is of significant practical value.

The fundamental frequency is defined as the frequency of the "events" of the EIG. An "event" is believed to represent the synchronized electrical activity of the cells in the islet. By analogy to an ECG, an "event" in EIG is comparable to a the heart cycle (the PQRST

comlex).

Although it is believed that EIG processing has not been performed by any entity but the owner the present patent application, one might attempt to detect the events directly, and then to calculate the fundamental frequency. The problem with this approach is that the shape and size of EIG "events" varies greatly, and therefore reliable and robust event detection is difficult to achieve.

In accordance with the present invention, the fundamental frequency of EIG events is determined directly, without first detecting the individual events themselves. All these algorithms must use an analysis window containing more than one event. The present invention utilizes techniques similar to those utilized to detect and estimate pitch in speech processing

The invention is based on two important biological discoveries. The first is that the EIG is generated by a functional pace maker. The second is that the EIG signal is *quasi-periodic* most of the time. Pitch detection algorithms are used, because of the essentially quasi-periodic nature of the EIG signal. By *quasi-periodic* we mean that (1) the intervals between successive events are not exactly identical, but may vary slightly and (2) the amplitude and shape of successive events may also exhibit some variance.

Several pitch detection algorithms were tested. Three of them achieved good results: Autocorrelation, Segmented Autocorrelation and Harmonic Peaks analysis. The preferred embodiments of the invention focus on algorithms that are based on the Autocorrelation methods.

The preferred version of the algorithm comprises the following steps:

- Detection of the non-EIG signals. The signal may include non-EIG segments, such as artifacts and silences. The signal is scanned and the non-EIG segments are marked and ignored.
    - The signal is divided into overlapping analysis windows, each four seconds long and each has a 75% overlap with the adjacent windows. The analysis window contains more than one event.
    - A modified form of an Autocorrelation transform of the type used for pitch detection in speech processing is applied to a single analysis window. This step is repeated for each analysis window.

- The fundamental frequency is derived from the autocorrelation values of the analysis window. Usually the fundamental frequency is indicated by the largest autocorrelation value. This step is repeated for each analysis window.
- A postprocessor is used to "smooth out" the results of all the individual analysis windows. The previously marked non-EIG segments (artifacts and silences) are added in this phase.

To produce the modified autocorrelation transform, the existing autocorrelation based algorithm was adapted to EIG in the following ways:

- An improved algorithm was devised for determining pitch from the autocorrelation values. The algorithm usually chooses the highest autocorrelation peak (value). In EIG we found that sometimes the true pitch is not represented by a peak, but rather by a valley between several adjacent peaks. An algorithm was devised to locate those cases, and to correctly estimate the pitch. We refer to this phenomena as a "volcano" shaped autocorrelation graph, because the center of the "mountain" is found on lower ground.
- A voiced/unvoiced decision mechanism was adapted from speech processing. The "unvoiced" EIG segments were defined as a non-signals (undecided segments). A postprocessor was used to decide on the pitch of those undecided segments. Although unvoiced speech segments do exist, "unvoiced" EIG segments are a virtual non-signal, and do not really exist.
- A special pre-processing algorithm was devised. The signal undergoes convolution so as to increase the width of the event. This is unlike speech pre-processing, which is aimed at enhancing the high amplitude portions and/or filtering out the formants. This preprocessing technique is referred to as "fattening".
- A very long analysis window of 4 seconds was used, in order to find frequencies ranging from 0.25 Hz to 5 Hz. In speech it is customary to use a window of about 30 milliseconds, in order to find frequencies ranging from 80 Hz to 300 Hz.

The invention also contemplates the use of a Segmented Autocorrelation algorithm. This is considered to be the best method for EIG, but other methods are also adequate. Segmented autocorrelation is described in "Pitch detection of speech signals using Segmented Autocorrelation"/ I. A. Atkinson, A. M. Kondoz, B.G. Evans/ Electronics Letters Vol. 31 No. 7 pp. 533-535/March 1995.

Brief Description of the Drawings

The foregoing brief description, as well as further objects, features, and advantages of the present invention will be understood more completely from the following detailed description of a presently preferred embodiment, with reference being had to the accompanying drawings, in which:

FIG. 1 is a functional block diagram showing an overview of the process of the preferred embodiment;

FIG. 2 is a flowchart describing the pre-detectors, the silence detector and the artifact detector;

FIG. 3 is a flowchart describing fundamental frequency estimation of an individual analysis window;

FIG. 4 is a flowchart expansion of one of the block 25 of FIG 3 and describes the decision algorithm of the fundamental frequency estimator; and

FIG. 5 is a flowchart describing the post-processing phase algorithms, which combine information from neighboring analysis windows in order to correct local estimation errors.

Detailed Description of the Preferred Embodiment

The preferred embodiment of the invention will now be described in detail with reference to the accompanying drawings. First a schematic overview of the preferred embodiment of a process and system for fundamental frequency estimation of EIG is presented in **FIG. 1**. The algorithm comprises of the following steps:

a. Detection of the non-EIG signals. The signal may include non-EIG segments, such as artifacts and silences. The signal is scanned and the non-EIG segments are marked and ignored. A silence detector **1** and an artifact detector **2** are used. An "artifact" is a

dominant interference noise signal, which severely corrupts the EIG signal.

b. The signal is divided into overlapping analysis windows. Each window is 4 seconds long and has a 75% overlap with the adjacent windows. The analysis window must contain more than one event. It is contemplated that the analysis window could be as much as forty times the interval between successive events.

c. The autocorrelation transform **4** is applied to a single analysis window. This step is repeated for each analysis window. pre-processing **3** is optional, and is not used in the preferred embodiment.

d. The fundamental frequency is derived from the autocorrelation values of the analysis window **5**. Usually the fundamental frequency is indicated by the largest autocorrelation value. A sureness measure **6** is computed for the estimated fundamental frequency of the analysis window. This step is repeated for each analysis window.

e. A postprocessor **7** is used to "smooth out" the results of all the individual analysis windows. The previously marked non-EIG segments (artifacts and silences) are added in this phase.

f. The output is the estimated fundamental frequency of the signal **8**.

The preferred embodiment of the invention includes software which preferably runs on a Pentium PC, using the Windows 95 operating system. The algorithm was implemented on the "Matlab" software by "The Mathworks Inc." The algorithm was written in the Matlab language, and runs within the Matlab program shell. It also requires the "Digital Signal Processing Toolbox" for Matlab, by "The Mathworks Inc."

FIG 2. is a flowchart describing the pre-detectors. The silence detector (**11 , 12 ,13**) involves two steps. In the first step **11** an amplitude related measure is computed for each second, and in the second step **12** the amplitude related measure is compared to a fixed threshold. "Sig" is the raw digital input signal. It is the raw signal recorded from the islet,

after an Analog to Digital conversion. In block 11 each one second window is examined. "Max(Sig)" is the maximum sample value within the examined one second window. "Min(Sig)" is the minimum of the samples' values within the examined one second window. As "Sig" is always a real number, the real maximum and minimum are computed. If the measure is below the threshold for more than 5 seconds, then the segment is classified as silence **13**. The threshold depends on the measurement equipment and environment. It also depends on the digitizing scale. In the preferred embodiment the maximum amplitude of the EIG signal is approximately 4000 amplitude units, so a threshold of 100 amplitude units is used. An "amplitude unit" is the amplitude difference between two adjacent quantization levels of the Analog to Digital converter. In the preferred embodiment one "amplitude unit" corresponds to 0.25 Micro-Volt of the original electrical signal. "Original" means before amplification.

The artifact detector (**14, 15, 16, 17**) involves two steps. In the first step **14** the signal is compared to an adaptive threshold. The adaptive threshold is computed using a 300 second long recording, by the following computation:

A high reference is defined as the 99.833 percentile of the histogram of the amplitude values of the 300 second long recording.

A low reference is defined as the 0.167 percentile of the histogram of the amplitude values of the 300 second long recording.

An amplitude reference is defined as the high reference minus the low reference.

A high threshold is defined as the high reference plus the amplitude reference.

A low threshold is defined as the low reference minus the amplitude reference.

The "histogram" used in block **14** is generated by simply sorting all the sample values ("amplitudes") of a 300 second long recording. The sorting is done from the smallest value to the largest value. Based on those sorted values the two references are derived. The "high reference" is the 99.833 percentile of the sorted values. The "low reference" is the 0.167 percentile of the sorted values. The term "histogram" refers to the sorting of the values, and can be replaced by the term "sorted amplitude values."

The second step **15** involves checking whether there are samples in which the signal's amplitude is above the high threshold or below the low threshold. If such samples are found then they are classified as containing an artifact **16**. The remaining samples **17** are not classified as an artifact or as a silence.

FIG. 3 contains a flowchart describing the steps that are performed on each analysis window. Each analysis window is 4 seconds long. Overlapping analysis windows are used. There is a 3 second overlap between two successive windows. Analysis windows containing either silences or artifacts are not analyzed. The analysis windows are described in block 21, and are represented mathematically by the following notation:

x(n) are the raw digital samples of the signal. We earlier referred to this raw input signal as "Sig." This is the same signal, only that here a more strict mathematical notation is used. The analysis window contains 4 seconds of signal. The sampling frequency ("FS") in the preferred embodiment is 100 Hz, therefore the analysis window contains 400 samples. This is marked by "N(Window length)=400." The first sample in the analysis window is *x(l)*, where "*l*" is the index of the sample. Therefore the last sample in the analysis window is *x(l+399)=x(l+N-1)*. Therefore the analysis window is described by the samples it contains from *x(l)* to *x(l+N-1)*.

Preprocessing **22** may be used, but it is not implemented in the preferred embodiment.

A rectangular window **23** is applied to the samples, and a normalized biased autocorrelation transform **24** is computed. It is represented mathematically by the following equation:

$$\varphi(m)=\frac{1}{\sum_{k=0}^{N-1}[x(k+1)w(k)]^2}\sum_{n=0}^{N-|m|-1}[x(n+1)w(n)][x(n+l+m)w(n+m)] \quad (1)$$

where "w(n)" is the windowing function." As "w(n)" is a rectangular window, as described in block 23, it is equivalent to "1" within the analysis window:

$$w(n)= \begin{array}{ll} 1 & 0\le n\le N-1 \\ 0 & \textit{Otherwise} \end{array}$$

The autocorrelation transform is further described in the book "Digital Processing of Speech Signals", L.R. Rabiner and R.W. Schafer, 1978, pp. 141-164. The fundamental frequency decision algorithm **25** is described in more detail in **FIG. 4**.

We will now refer to **FIG. 4** and later return to **FIG. 3**.

FIG. 4 is a flowchart describing the fundamental frequency decision algorithm. Actually it decides on the fundamental period, from which the fundamental frequency can be derived. An improved algorithm was devised for determining the fundamental frequency from the autocorrelation values. In typical algorithms the highest autocorrelation peak (value) is usually chosen. In EIG, it was found that sometimes the true pitch is not represented by a peak, but rather by a valley between several adjacent peaks. An algorithm was devised to locate those cases, and to estimate the pitch correctly. We refer to this phenomenon as a "volcano" shaped autocorrelation graph, because the center of the "mountain" is found on lower ground.

The input to the decision algorithm is a vector containing the autocorrelation coefficients **31**. Steps **32** and **33** find the 5 highest extreme points within the allowed frequency range. A "volcano" effect detector **34** checks first whether one of the highest peaks is found in a suspected "volcano" area. If such a peak is found, it's index (*i*) is passed on in order to check the peak's amplitude **35** compared to the amplitude of the highest peak. If the result is positive then a "volcano" is detected **36** and the estimated fundamental period is half of the autocorrelation lag corresponding to the highest peak. The autocorrelation is represented by equation (1) above. *m* is the "autocorrelation lag." It is the lag between the two segments on which the correlation is computed. The first segment is $x(n+l)$ to $x(n+l+N-|m|-1)$ and the second segment is $x(n+l+m)$ to $(x+l+m+N-|m|-1)$. Also, see "Digital Processing of Speech Signals", L.R. Rabiner and R.W. Schafer, 1978, pp. 141-164.

A pitch halving detection algorithm **37** first checks the ratio of the

autocorrelation coefficients' lag **37**, and then their amplitudes **38**. If one of the highest peaks fulfills both those conditions then it is chosen as the estimated fundamental period **39**. If both the "volcano" detector and the pitch halving detector produced negative results, then the estimated fundamental period is assumed to be the lag of the highest autocorrelation peak **40**. The output of the fundamental period decision algorithm of **FIG. 4** is the estimated fundamental period. This output is returned to block 26 in **FIG. 3**.

A "voiced" decision mechanism **26** (**Fig. 3**) is used to decide whether the fundamental frequency should be estimated in the current analysis window. If the maximum autocorrelation coefficient in the allowed lag range (a lag of 20 to 333 samples) is below 0.3, then the analysis window is classified as "unvoiced", and no fundamental frequency is estimated **27**. In that case a sureness grade of zero is given to the analysis window.

The voiced / unvoiced decision mechanism was adapted from speech processing. The "unvoiced" EIG segments were defined as non-signals (undecided segments). The postprocessor will be used in later stages to decide on the fundamental frequency of those undecided segments. Note that unvoiced speech segments do exist, while "unvoiced" EIG segments are a virtual non-signal, and do not really exist.

If the current analysis window is not classified as "unvoiced" then the estimation process continues, and a sureness grade is calculated for the current analysis window **28**. A higher sureness grade indicates that there is a higher probability that the fundamental frequency was estimated correctly. For each analysis window several outputs **29** are returned:

1. The estimated fundamental period- this value is not returned if the analysis window is classified as "unvoiced";
2. A "voiced"/"unvoiced" decision- specifies whether the fundamental period was estimated in the analysis window; and
3. A sureness grade- this value is not returned if the analysis window is classified as "unvoiced".

FIG. 5 describes the final stage of the estimation process: the postprocessor. The postprocessor combines all the acquired data **41** into a fundamental frequency estimate of the raw signal. The postprocessor operates on a 300 second long recording of the raw signal. The first step **42** is to convert all the estimated fundamental period values into estimated fundamental frequency ("Pitch") values. The output of this stage is a fundamental

frequency estimate, in Hertz, for every "voiced" analysis window. The next step **43** inserts the previously detected silence segments **1** into the fundamental frequency estimation results. The fundamental frequency is assigned a value of 0 (Hz) in all windows containing only silences. All analysis windows containing an unlikely fundamental frequency estimate are marked as "unvoiced" in the next step **44**.

The next step **45** assigns a fundamental frequency ("pitch") value to the "unvoiced" segments. The postprocessor loops once over all the analysis windows. It assigns Pitch values to all "unvoiced" windows (windows containing artifacts are also treated as "unvoiced"). Pitch values are derived from an average of the pitch values of the neighboring windows. Some minor data dependent modifications can be added in order to create a smarter averaging method, but those are minor changes which are very data dependent. A pitch halving / doubling error correcting mechanism is then applied **46**. The algorithm loops once over all the analysis windows. If the Pitch of the current window is half or double the average of the neighboring windows, then the current Pitch is taken as a smart average of the neighbors. The term "smart averaging" refers to the average of an ensemble of numbers, after the extreme values are removed. For example: We can define a "smart average" of 8 numbers in the following way:

1. Remove the maximal and minimal numbers and
2. Compute the average of the remaining 6 numbers.

This "smart averaging" method is used in order to achieve more stable and robust results.

The final step **47** looks for an analysis window having a pitch which is significantly different than its neighbors. The algorithm loops once over all the analysis windows. If the Pitch of the current window, is 35% greater or smaller than the average of the neighboring windows, then the current Pitch is taken as a smart average of the neighbors.

The final output **48** of the entire fundamental frequency estimation process is a fundamental frequency value for each analysis window.

Although a preferred embodiment of the invention has been disclosed for illustrative purposes, those skilled in the art will appreciate that many additions, modifications and substitutions are possible without departing from the scope and spirit of the invention. For example, the principles and applications of the invention are not limited to the particular biological phenomenon described. They could be utilized equally well, for example, for measuring an optical signal from living cells of a muscle or the electrical signals of neurons,

or various signals produced by similar or other biological micro-structures. In particular, it is contemplated that the invention could find utility in any application where a cell or other biological micro-structure is moved outside its natural environment and used as a biological sensor.

I CLAIM:

1. A method for monitoring biological micro-structure activity which produces detectable signals characterizing events, comprising the steps of estimating the fundamental frequency of the occurrence of events from the detectable signals, without detecting the occurrence of individual events.

2. The method of claim 1 wherein events are analyzed during an analysis window which spans more than one event.

3. The method of any of claims 1 or 2 wherein the events are signals produced by biological micro-structures which are displaced from their original environment.

4. The method of any of claims 1 or 2 wherein the events are signals produced by living cells.

5. The method of claim 4 wherein the events are signals produced by the Islets of Langerhans.

6. The method of any one of claims 1or 2 wherein the estimating step includes an autocorrelation operation.

7. The method of claim 6 further including one of the following steps:

estimating the fundamental frequency based upon a lower autocorrelation value disposed among several adjacent peaks;

treating "unvoiced" segments of the detectable signal as undecided as to pitch and estimating the pitch of those segments through subsequent processing;

seeking to estimate the fundamental frequency in the range of .25 to 5 Hertz;

utilizing an analysis window duration in the range of several seconds;

performing a pre-processing operation which has the effect of increasing the effective duration of an event; and

utilizing an autocorrelation process which performs segmented

autocorrelation.

8. The method of Claim 1 further comprising the step of using the number of "unvoiced" windows within a predetermined time as a measure of a blood constituent level of a patient.

9. The method of Claim 1 further comprising the step of using a sureness grade as measure of a blood or tissue constituent level of a patient.

10. The method of Claim 1 further comprising the step of using the fundamental frequency as a measure of a blood or tissue constituent level of a patient.

11. The method of Claim 1 wherein the blood constituent level is the blood glucose level in the vicinity of the biological micro-structure.

12. The method of claim 1 wherein the events are electrical signals produced by living cells in the Islets of Langerhans used as a probe within a patient and the fundamental frequency estimate is used as a measure of blood glucose level of the patient.

13. The method of any one of claims 2, wherein an analysis window spans a duration of up to 40 times the interval between successive events..

14. In a system for monitoring biological micro-structure activity which produces detectable signals characterizing events, a sensor capable of receiving the sensible signals and a processor including a module for estimating the fundamental frequency of the occurrence of events from the detectable signals, without first detecting the occurrence of individual events.

15. The system of claim 14 wherein the processor further comprises a module for producing an analysis window during which events are analyzed, the analysis window spanning more than one event.

16. The system of Claim 14 or 15 wherein the module for estimating

includes components to perform an autocorrelation operation.

17. The system of Claim 16 wherein the module for estimating further includes one of the following submodules:

a submodule which estimates the fundamental frequency based upon a lower autocorrelation value disposed among several adjacent peaks;

a sub-module which identifies "unvoiced" segments of the detectable signal as undecided as to pitch, the pitch of those segments being estimated by a subsequent processing submodule;

a submodule which controls the estimate of the fundamental frequency to be in the range of .25 to 5 Hertz;

a submodule controlling the analysis window to have a duration in the range of several seconds; and

a submodule performing a pre-processing operation which has the effect of increasing the effective duration of an event.

18. The system of Claim 14 or 15 wherein the processor is constructed to perform a segmented autocorrelation process.

19. The system of claim 14 or 15 wherein the sensor is a probe capable of detecting signals emitted by living cells in the Islets of Langerhans, the frequency estimate being an indication of blood glucose level of a patient in which those cells are present.

20. The system of any one of claims 15, wherein an analysis window spans a duration of up to 40 times the interval between successive events..

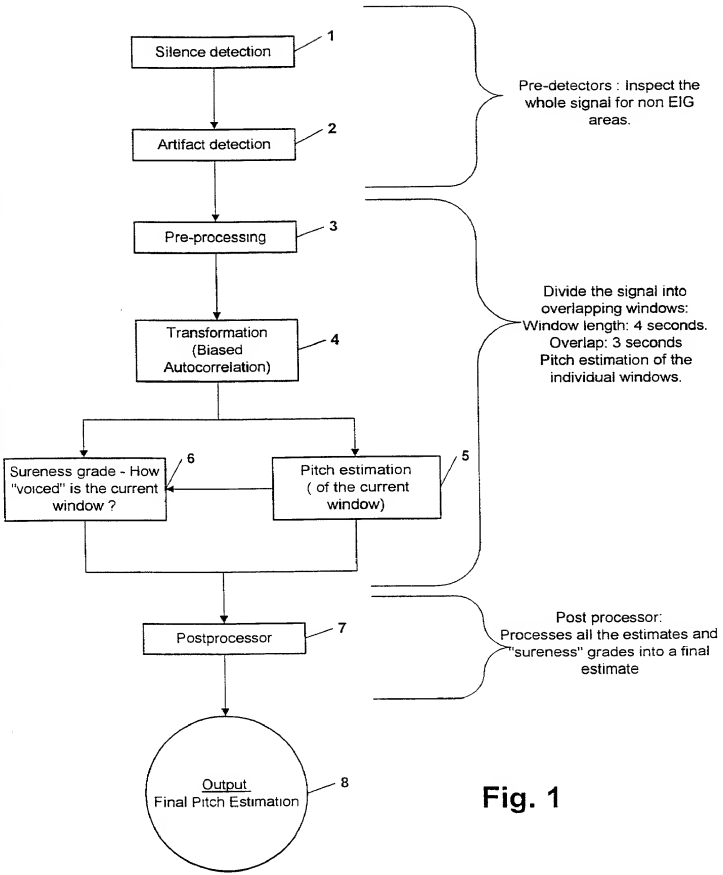
Silence detection
1
Artifact detection
2
Pre-detectors : Inspect the whole signal for non EIG areas.
Pre-processing
3
Transformation (Biased Autocorrelation)
4
Divide the signal into overlapping windows:
Window length: 4 seconds.
Overlap: 3 seconds
Pitch estimation of the individual windows.
Sureness grade - How "voiced" is the current window ?
6
Pitch estimation (of the current window)
5
Postprocessor
7
Post processor:
Processes all the estimates and "sureness" grades into a final estimate
Output
Final Pitch Estimation
8

Fig. 1

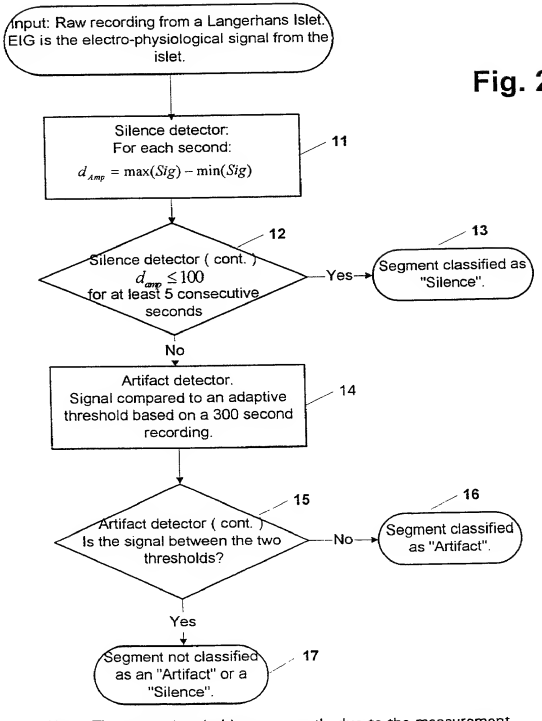

Fig. 2

Note: The exact thresholds vary greatly due to the measurement methods, the measurement equipment, and the conditions of the experiment. The thresholds must be fitted manually for each experimental set-up.

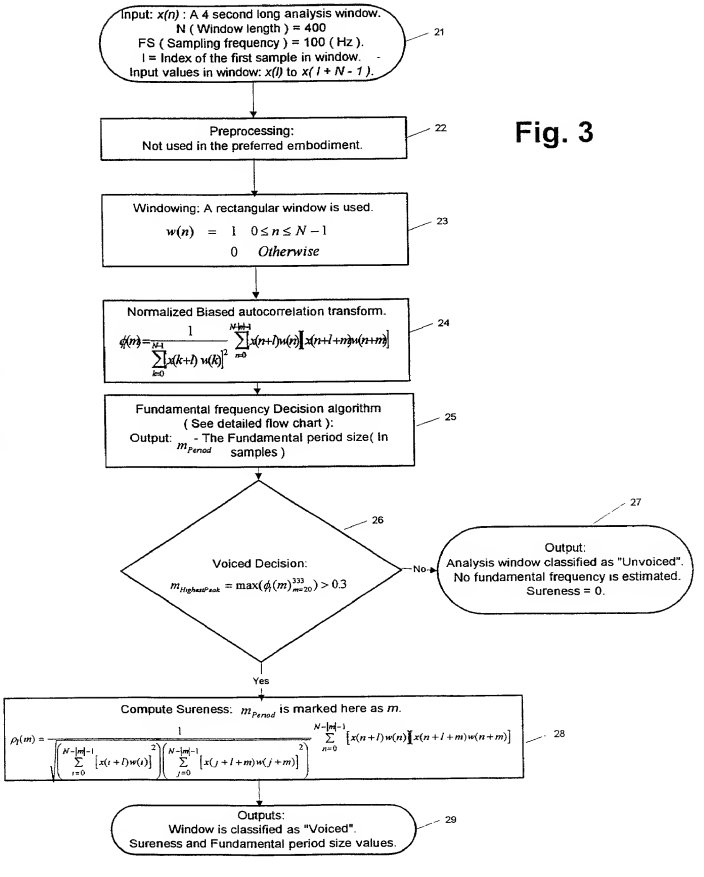
Input: x(n) : A 4 second long analysis window.
N (Window length) = 400
FS (Sampling frequency) = 100 (Hz).
I = Index of the first sample in window.
Input values in window: x(I) to x(I + N - 1).
21
Preprocessing:
Not used in the preferred embodiment.
22
Windowing: A rectangular window is used.
w(n) = 1 0 ≤ n ≤ N − 1
0 Otherwise
23
Normalized Biased autocorrelation transform.
24
Fundamental frequency Decision algorithm
(See detailed flow chart):
Output: - The Fundamental period size(In samples)
25
Voiced Decision:
26
No
Output:
Analysis window classified as "Unvoiced".
No fundamental frequency is estimated.
Sureness = 0.
27
Yes
Compute Sureness: is marked here as m.
28
Outputs:
Window is classified as "Voiced".
Sureness and Fundamental period size values.
29

Fig. 3

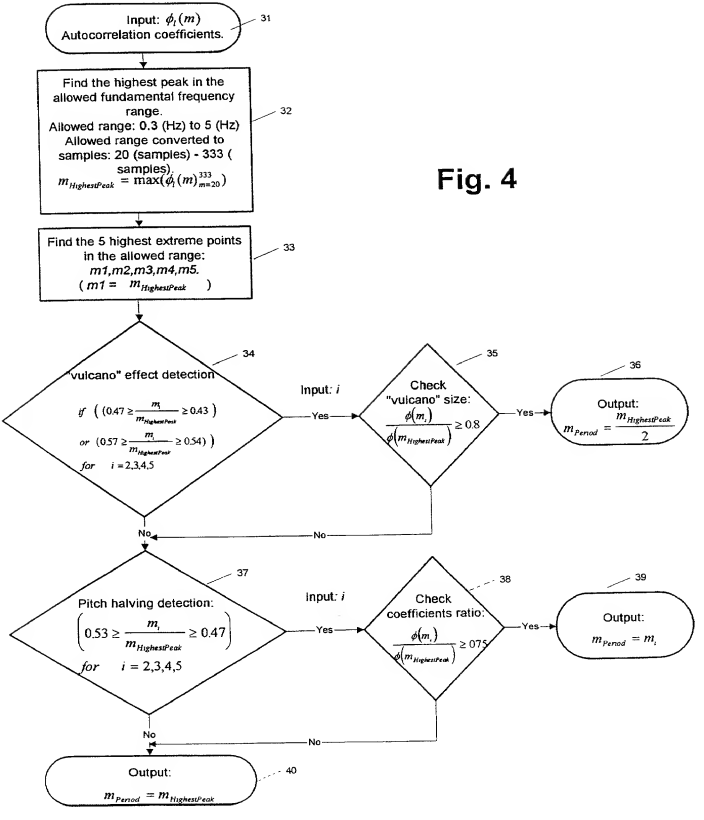
Input: $\phi_i(m)$ Autocorrelation coefficients.
31
Find the highest peak in the allowed fundamental frequency range.
Allowed range: 0.3 (Hz) to 5 (Hz)
Allowed range converted to samples: 20 (samples) - 333 (samples).
$m_{HighestPeak} = \max(\phi_i(m)_{m=20}^{333})$
32
Find the 5 highest extreme points in the allowed range: m1,m2,m3,m4,m5.
(m1 = $m_{HighestPeak}$)
33
"vulcano" effect detection
34
if $\left(0.47 \geq \frac{m_i}{m_{HighestPeak}} \geq 0.43\right)$
or $\left(0.57 \geq \frac{m_i}{m_{HighestPeak}} \geq 0.54\right)$
for i = 2,3,4,5
Input: i
Yes
No
Check "vulcano" size:
35
$\frac{\phi(m_i)}{\phi(m_{HighestPeak})} \geq 0.8$
Yes
No
Output:
36
$m_{Period} = \frac{m_{HighestPeak}}{2}$
Pitch halving detection:
37
$\left(0.53 \geq \frac{m_i}{m_{HighestPeak}} \geq 0.47\right)$
for i = 2,3,4,5
Input: i
Yes
No
Check coefficients ratio:
38
$\frac{\phi(m_i)}{\phi(m_{HighestPeak})} \geq 075$
Yes
No
Output:
39
$m_{Period} = m_i$
Output:
40
$m_{Period} = m_{HighestPeak}$

Fig. 4

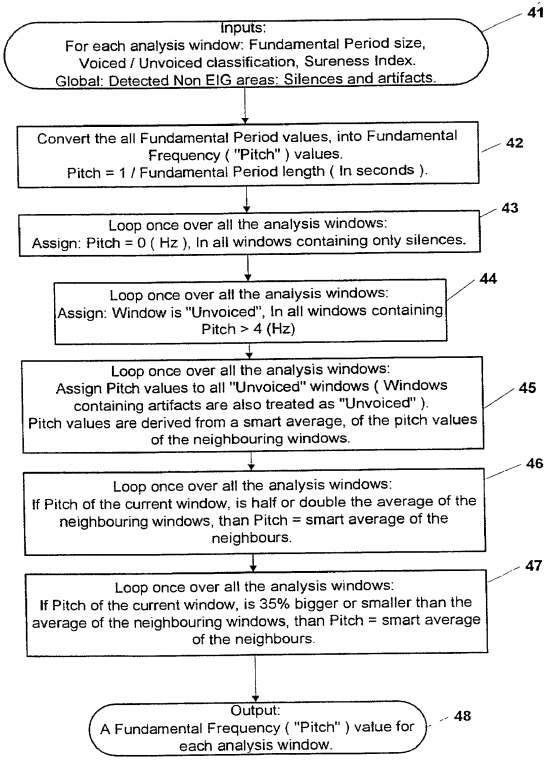
Inputs:
For each analysis window: Fundamental Period size, Voiced / Unvoiced classification, Sureness Index.
Global: Detected Non EIG areas: Silences and artifacts.
41
Convert the all Fundamental Period values, into Fundamental Frequency ("Pitch") values.
Pitch = 1 / Fundamental Period length (In seconds).
42
Loop once over all the analysis windows:
Assign: Pitch = 0 (Hz), In all windows containing only silences.
43
Loop once over all the analysis windows:
Assign: Window is "Unvoiced", In all windows containing Pitch > 4 (Hz)
44
Loop once over all the analysis windows:
Assign Pitch values to all "Unvoiced" windows (Windows containing artifacts are also treated as "Unvoiced").
Pitch values are derived from a smart average, of the pitch values of the neighbouring windows.
45
Loop once over all the analysis windows:
If Pitch of the current window, is half or double the average of the neighbouring windows, than Pitch = smart average of the neighbours.
46
Loop once over all the analysis windows:
If Pitch of the current window, is 35% bigger or smaller than the average of the neighbouring windows, than Pitch = smart average of the neighbours.
47
Output:
A Fundamental Frequency ("Pitch") value for each analysis window.
48

Fig. 5

COMBINED DECLARATION FOR PATENT APPLICATION AND POWER OF ATTORNEY
(Includes Reference to PCT International Applications)

ATTORNEY DOCKET NUMBER
2013/1E271-US1

As a below named inventor, I hereby declare that.

My residence, post office address and citizenship are as stated below next to my name.

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed for and which a patent is sought on the invention entitled.

FREQUENCY ESTIMATION OF ELECTRO-ISLET GRAPHY

the specification of which (check only one item below):

[] is attached hereto

[] was filed as United States application

Serial No. _____

on _____

and was amended

on _____ (if applicable)

[X] was filed as PCT international application

Number PCT/US99/11973

on May 28, 1999

and was amended under PCT Article 19

on _____ (if applicable).

I hereby state that I have reviewed and understand the contents of the above-identified specification, including the claims as amended by any amendment referred to above.

I acknowledge the duty to disclose information which is material to the examination of this application in accordance with Title 37, Code of Federal Regulations, §1.56(a).

I hereby claim foreign priority benefits under Title 35, United States Code, §119 of any foreign application(s) for patent or inventor's certificate or of any PCT international application(s) designating at least one country other than the United States of America listed below and have also identified below any foreign application(s) for patent or inventor's certificate or any PCT international application(s) designating at least one country other than the United States of America filed by me on the same subject matter having a filing date before that of the application(s) of which priority is claimed:

PRIOR FOREIGN/PCT APPLICATION(S) AND ANY PRIORITY CLAIMS UNDER 35 U.S.C. 119:

COUNTRY (if PCT indicate PCT)	APPLICATION NUMBER	DATE OF FILING (day, month, year)	PRIORITY CLAIMED UNDER 35 U.S.C. 119
United States	60/087,026	28 May 1998	[X] YES [] NO
			[] YES [] NO
			[] YES [] NO
			[] YES [] NO
			[] YES [] NO

US

Combined Declaration for Patent Application and Power of Attorney (Continued)
(Includes Reference to PCT International Applications)

ATTY'S DOCKET NUMBER
2013/1E271-US1

I hereby claim the benefit under Title 35, United States Code, §120 of any United States application(s) or PCT international application(s) designating the United States of America that is/are listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in that/those prior application(s) in the manner provided by the first paragraph of Title 35, United States Code §112, I acknowledge the duty to disclose material information as defined in Title 37, Code of Federal Regulations, §1.56(a) which occurred between the filing date of the prior application(s) and the national or PCT international filing date of this application:

PRIOR U.S. APPLICATIONS OR PCT INTERNATIONAL APPLICATIONS DESIGNATING THE U.S. FOR BENEFIT UNDER 35 U.S.C. 120:

U.S APPLICATIONS		STATUS (Check one)		
U.S APPLICATION NUMBER	U.S. FILING DATE	PATENTED	PENDING	ABANDONED

PCT APPLICATIONS DESIGNATING THE U.S.

PCT APPLICATION NO.	PCT FILING DATE	U.S SERIAL NUMBER ASSIGNED (if any)

POWER OF ATTORNEY: As a named inventor, I hereby appoint the following attorney(s) and/or agents to prosecute this application and transact all business in the Patent and Trademark Office connected therewith. Morris Reison #15,108, Gordon D. Coplein #19,165, William F. Dudine, Jr. #20,569, Michael J. Sweedler #19,937, S. Peter Ludwig #25,351, Paul Fields #20,298, Joseph B. Lerch #26,936, Melvin C. Garner #26,272, Ethan Horwitz #27,646, Beverly B. Goodwin #28,417, Adda C. Gogoris #29,714, Martin E. Goldstein #20,869, Bert J. Lewen 19,407, Henry Sternberg #22,408, Peter C. Schechter #31,662, Robert Schaffer #31,196 Robert C. Sullivan, Jr. #30,439, and Joseph R. Robinson #33,448

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2	POST OFFICE ADDRESS	POST OFFICE ADDRESS	CITY	STATE & ZIP CODE/COUNTRY
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3	POST OFFICE ADDRESS	POST OFFICE ADDRESS	CITY	STATE & ZIP CODE/COUNTRY

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patents issuing thereon.

SIGNATURE OF INVENTOR 201	SIGNATURE OF INVENTOR 202	SIGNATURE OF INVENTOR 203
DATE: 12/6/2000	DATE	DATE